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### Treatment of immobilisation hypercalcaemia in acute intermittent porphyria: experience from three cases

When acute intermittent porphyria presents as an immobilising polyneuropathy, recovery is often prolonged and fraught with medical complications. Three such patients are described, all of whom developed severe hypercalcaemia during the course of their illness. The safety of calcium lowering agents in porphyria is not established and our experience is described.

Patient 1, a previously fit 16 year old Tunisian girl, was transferred from her home town having developed profound global weakness after treatment of two generalised convulsions with phenobarbitone. On admission she was tachycardic and unable to stand unsupported. She was areflexic except at the ankles. Sensation was diminished in a bathing trunk distribution. The clinical impression of acute intermittent porphyria was confirmed by laboratory investigations which included raised urinary concentrations of total porphyrins, porphobilinogen, and  $\delta$ -amino laevulinic acid (600, 146, and 138  $\mu\text{mol/l}$ , respectively—normal ranges, 0–300, 0–11, 1–34  $\mu\text{mol/l}$ ). In keeping with acute intermittent porphyria, serum concentrations of porphobilinogen deaminase were low at 17.4 units (normal range 30–54) and she had a leucocytosis ( $22 \times 10^9/\text{l}$ ), mild uraemia (8.4 mmol/l), deranged liver function (ALT 337  $\mu\text{l}$ , ALP 190  $\mu\text{l}$ ), and mild hyponatraemia (132 mmol/l).

Her initial progress was complicated by the development of septicaemia and subsequent progressive dysphasia due to a large left parietal lobe abscess. Surgical treatment of this and subsequent appropriate antibiotic therapy (imipenem) coincided with an apparent relapse of the porphyria. Increasing global weakness necessitated ventilation and was associated with a significant rise in urinary porphobilinogen excretion.

Her subsequent course was satisfactory although she remained confined to bed, requiring intermittent overnight ventilatory assistance. However, five months after admission, she developed spontaneous severe hypercalcaemia (4.02 mmol/l, corrected for a serum albumin of 32 g/l) in the presence of normal phosphate, thyroxine, parathyroid hormone, and 25-hydroxycalciferol concentrations. As 24 hour urinary calcium excretion was raised (25.3 mmol, normal range up to 8 mmol), this was presumed to be a consequence of increased bone turnover associated with immobility. Given the subsequent failure of vigorous hydration and loop diuretics to lower calcium concentrations, bisphosphonate therapy—a recognised treatment for immobilisation hypercalcaemia<sup>1,2</sup> was considered. Because the safety of such drugs in porphyria is unknown, baseline urinary porphyrin excretion was monitored continuously for five days before the intravenous administration of a single dose of disodium pamidronate (10 mg). The drug was highly

effective at reducing the hypercalcaemia (figure) and, although associated with a small transitory rise in urinary porphobilinogen, produced no signs of clinical deterioration.

The patient required a further bolus of bisphosphonate two months later before being transferred for further rehabilitation in the United States.

Patient 2, a previously fit 21 year old woman, with a short history of abdominal pain and vomiting was prescribed metronidazole, a cephalosporin, and trimethoprim-sulphamethoxazole as treatment for presumed pelvic inflammatory disease. Twenty four hours later, she experienced a generalised convulsion and subsequently developed rapidly progressive global weakness with respiratory and bulbar involvement due to a severe axonal neuropathy. Laboratory investigations including urinary analysis for porphobilinogen confirmed acute intermittent porphyria. She required ventilatory support for two months and was confined to bed for a further six. Progress was complicated by pulmonary tuberculosis, discovered shortly after admission and treated with triple therapy for nine months (streptomycin, ethambutol, and isoniazid).

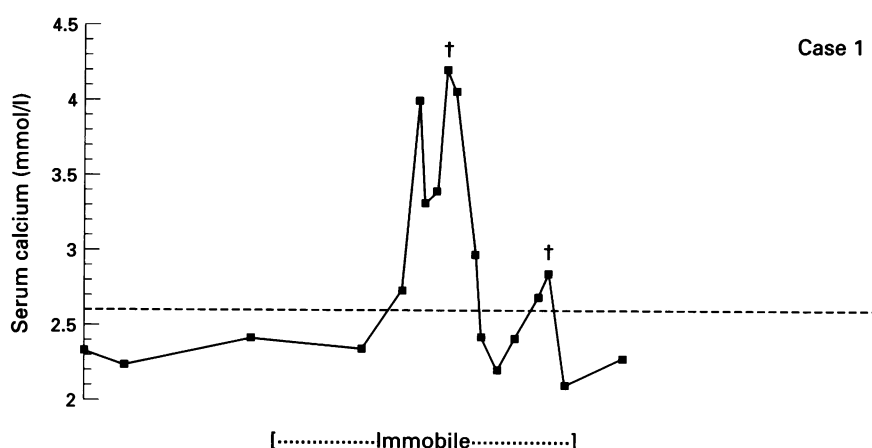
One month after admission, she developed hypercalcaemia (3.96 mmol/l, corrected value) which persisted despite high fluid intake (6 l/day) and a low calcium diet. As with patient 1, plasma concentrations of phosphate, thyroxine, 25-hydroxycalciferol, and parathyroid hormone were all

normal but urinary calcium excretion was greatly increased. On the basis of a slightly abnormal radioisotopic parathyroid scan, surgical exploration of all four parathyroid glands was undertaken, disclosing normal histology in all.

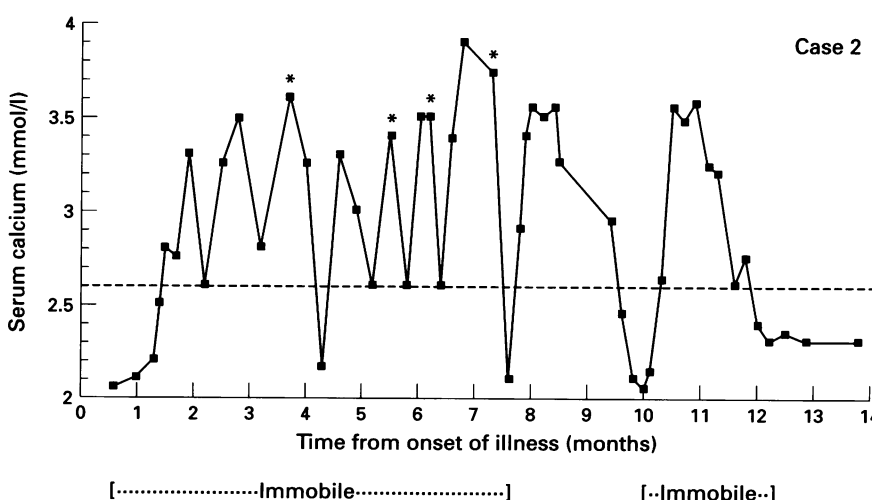
As immobilisation hypercalcaemia associated with Guillain-Barré syndrome has been successfully treated with steroids,<sup>3</sup> the patient was given repeated short courses of oral prednisolone (40 mg daily for two days). This strategy was effective at reducing the hypercalcaemia to acceptable concentrations (figure). She was also given a single dose of salmon calcitonin (100 MRC units), previously reported to be effective in immobilisation hypercalcaemia.<sup>4</sup> This lowered calcium concentrations from 3.05 to 2.47 mmol/l with no obvious relapse of the porphyria.

Together with her improving mobility, the hypercalcaemia resolved. A short lived relapse 10 months after admission produced transient hypercalcaemia which, once again, improved when mobility returned (figure).

Patient 3, a 20 year old woman, was admitted as a surgical emergency with abdominal pain after the injection of a depot contraceptive preparation. Over the next five days she developed profound flaccid tetraparesis and required ventilatory assistance for the next two months. Previously, she had been generally well but was known to have had generalised convulsions as a child and had developed an unexplained transient



Case 1



Case 2

Time course of development of hypercalcaemia with respect to spells of severe immobility and treatment with disodium pamidronate in patient 1 (†) and prednisolone (\*) in patient 2. Serum calcium concentrations are corrected for albumin concentration.

acute psychotic illness after the removal of a normal appendix, when aged 18.

The diagnosis of acute intermittent porphyria was confirmed by raised urinary porphobilinogen concentrations and reduced serum porphobilinogen deaminase activity. Her subsequent progress while ventilated was complicated by repeated chest infections and psychiatric problems.

Soon after weaning from the ventilator, she developed hypercalcaemia (2.87 mmol/l, corrected value), that was refractory to simple lowering measures. An intravenous bolus of disodium pamidronate (15 mg) reduced calcium concentrations to 2.4 mmol/l but was associated with increasing weakness 36 hours later, necessitating ventilatory support for two days. Over the next four months she remained immobile and her calcium rose slowly to 3.19 mmol/l. On this occasion, oral bisphosphonate was prescribed which lowered the calcium to 2.78 mmol/l. Despite the lack of objective clinical deterioration, the patient complained of worsening weakness and discharged herself against advice. One year after her illness she is known to have moderate tetraparesis but is able to walk with supports.

Although acute intermittent porphyria can cause various metabolic abnormalities, immobilisation hypercalcaemia is not widely recognised. It remains uncertain whether patients with acute intermittent porphyria are particularly prone to developing this complication as in other, more common, polyneuropathies with a potentially similar range of severity and duration such as Guillain-Barré syndrome, it is reported only rarely and with a male preponderance.<sup>3</sup>

Prolonged hypercalcaemia due to immobilisation and increased bone turnover is important to recognise and treat because of the potential for complications such as nephrocalcinosis, osteoporosis, and further axonal damage. In the context of severe acute intermittent porphyria, a strategy of early mobilisation is rarely possible and drug therapy is potentially hazardous. From our experience, repeated courses of steroids seem effective but are likely to have undesirable long term side effects such as reduced total body calcium. On the basis of a single injection of calcitonin, this also seems effective and safe. Bolus intravenous infusions of disodium pamidronate are likely to be the most efficient at lowering plasma calcium concentrations for prolonged periods but may not be safe at doses higher than 10 mg. If the drug is given, appropriate back up for ventilatory support needs to be readily available should clinical deterioration ensue.

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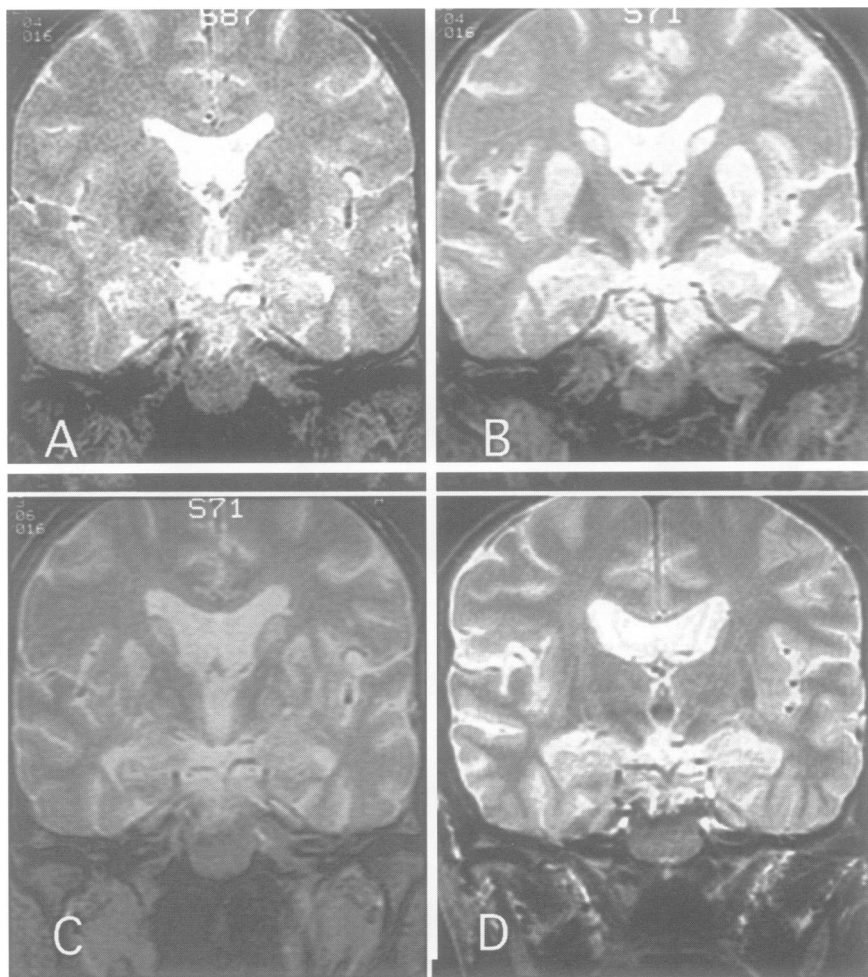
### Extrapontine myelinolysis presenting with parkinsonism as a sequel of rapid correction of hyponatraemia

We report an unusual case of a patient with extrapontine myelinolysis without central pontine myelinolysis, who presented with parkinsonism after the rapid correction of hyponatraemia.

A 53 year old man was admitted to our hospital because of gait and speech disturbance. Five days before surgery (see below), he developed a headache. The headache gradually increased in intensity and visual acuity decreased in his left eye on the day before surgery. Physical examination showed bitemporal hemianopsia. Brain CT disclosed a hyperdense lesion in the sellar region, and MRI showed a pituitary mass with isosignal intensity on T1 and slightly high signal intensity on T2 weighted images, raising the optic chiasm. Pituitary apoplexy induced by

pituitary tumour was diagnosed and a trans-sphenoidal hypophysectomy was performed on 25 April 1994. Histopathology of the pituitary tissue removed was consistent with a chromophobic adenoma. His level of consciousness after surgery was good. Intractable diabetes insipidus developed 18 days later, associated with hyponatraemia (serum sodium 103 mEq/l). He was given 8500 ml physiological saline intravenously over three days. Serum sodium was corrected to 126 mEq/l. The next day, he experienced dysarthria, bradykinesia, and shuffling gait. His symptoms worsened and six months after his surgery, he had a mask-like face, bradykinesia, difficulty in protruding his tongue, dysarthria, and dystonia in his fingers. Neither cogwheel rigidity nor tremor was present. He showed a parkinsonian posture. His walking was reduced to a shuffle, there was hesitation on starting and turning, and kinesie paradoxe was present. Tendon reflexes were normal and plantar responses were flexor. He had mild anaemia (haemoglobin 11.0 g/dl) and normal antidiuretic and thyroid hormone concentrations.

Brain MRI before surgery had disclosed no abnormal findings in the pons and basal ganglia (figure, A). Seven days after his clinical deterioration MRI showed increased signal intensities on the coronal T2 weighted images in the putamen and caudate nuclei



T2 weighted MRI during the clinical course of the patient's illness (coronal section). (A) Basal ganglia were intact before surgery (1.5T, TR/TE 2000/80 ms). (B) Increased signal intensities in the putamen and caudate nuclei on the seventh day after clinical deterioration (1.5T, TR/TE 2000/80 ms). (C) High signal intensities were decreased on the 30th day (1.5T, TR/TE 2000/80 ms). (D) Atrophy of the putamen and caudate nuclei and dilatation of lateral ventricles 10 months later, after development of parkinsonism (0.5T, TR/TE 2000/100).